EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S101	97950	gusperimus adh hydrochloride	USPAT	OR	OFF	2006/05/17 13:37
S102	11	gusperimus adj hydrochloride	USPAT	OR	OFF	2006/05/17 13:38
S103	11	gusperimus and vasculitis	USPAT	OR	OFF	2006/05/17 13:56
S104	198	514/551.ccls.	USPAT	OR	OFF	2006/05/17 13:58
S105	2	S104 and (deoxyspergualin or gusperimus)	USPAT	OR	OFF	2006/05/17 14:24
S106	299	(15-deoxyspergualin or gusperimus)	USPAT	OR	OFF	2006/05/17 13:57
S107	755	514/419.ccls.	USPAT	OR	OFF	2006/05/17 14:09
S108	1	S107 and S106	USPAT	OR	OFF	2006/05/17 13:58
S109	1	S107 and deoxyspergualin	USPAT	OR	OFF	2006/05/17 13:58
S110	349	514/634.ccls.	USPAT	OR	OFF	2006/05/17 14:10
S111	2	S110 and deoxyspergualin	USPAT	OR	OFF	2006/05/17 13:59
S112	1	S110 and spergualin	USPAT	OR	OFF	2006/05/17 14:02
S113	493	(deoxyspergualin or spergualin)	USPAT	OR	OFF	2006/05/17 14:10
S114	110	514/614.ccls.	USPAT	OR	OFF	2006/05/17 14:13
S115	0	S114 and spergualin	USPAT	OR	OFF	2006/05/17 14:09
S116	107	514/540.ccls.	USPAT	OR	OFF	2006/05/17 14:10
S117	3	S116 and S113	USPAT	OR	OFF	2006/05/17 14:10
S118	571	514/616.ccls.	USPAT	OR	OFF	2006/05/17 15:29
S119	6	S118 and spergualin	USPAT	OR	OFF	2006/05/17 14:13
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S121	367	514/114.ccls.	USPAT	OR	OFF	2006/05/17 15:30

EAST Search History

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S140	8003	less adj often	US-PGPUB; USPAT	OR	OFF	2006/05/18 15:27
S141	51	administered adj3 less adj often	US-PGPUB; USPAT	OR	OFF	2006/05/18 18:34
S142	281	dorzolamide	US-PGPUB; USPAT	OR	OFF	2006/05/18 18:34
S143	222	S142 and timolol	US-PGPUB; USPAT	OR	OFF	2006/05/18 18:35

EAST Search History

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S145	5069	(single adj composition)	US-PGPUB; USPAT	OR	OFF	2006/05/18 18:45
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S147	135	(single adj composition) and ophthalmic	USPAT	OR	OFF	2006/05/18 18:38
S148	105	S147 and (separately or seqential or subsequently)	USPAT	OR	OFF	2006/05/18 18:39
S149	21	S148 and (glaucoma or iop)	USPAT	OR	OFF	2006/05/18 18:39
S150	4355	S145 and combination	US-PGPUB; USPAT	OR	OFF	2006/05/18 18:45
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S161	28	S159 and (single adj composition)	USPAT	OR	OFF	2006/05/18 18:59
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EAST Search History

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S181	303	dorzolamide	US-PGPUB; USPAT; DERWENT	OR	OFF	2006/05/18 22:03
S182	224	S181 and timolol	US-PGPUB; USPAT; DERWENT	OR	OFF	2006/05/18 22:03

EAST Search History

S183	213	S182 and combination	US-PGPUB; USPAT; DERWENT	OR	OFF	2006/05/18 22:04
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S186	8	S184 and single	USPAT; DERWENT	OR	OFF	2006/05/18 22:04

Transdermal formulation and evaluation of timolol maleate.

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Summary
Transdermal delivery of **timolol** meliate was tried for both reservoir as well as matrix system. The physically stable patches regarding drug contents, tensile strength, toughness and WVT were found for PVA10 and HE2 formulation. Both patches follows diffusion controlled drug permeation and high permeation with PVA10 while reservoir system follows zero order permeation kinetics.

Introduction
Timolol maleate is a beta adrenoceptor-blocking agent used in treatment of cardiovascular diseases like myocardial infarction, angina pectoris, hypertension, respiratory complications and migraine. It is 8-10 times potent than propranolol 1. The main limitation of therapeutic effectiveness of **timolol** maleate is its higher frequency of drug dosing and short biological half-life, high first pass metabolism and poor bioavailability by oral route. . It is rapidly absorbed from gastrointestinal tract with **peak plasma concentration** of 5-10 ng/ ml after 1 hr2, it is metabolized up to 80% in liver with a mean half-life of 2.0-2.5 hr.3, thus necessitating frequent administration of larger doses to maintain therapeutic drug level. Therefore, To maintain effective **plasma concentration** and to avoid sub therapeutic and toxic **concentration**, a continuous delivery of **timolol** maleate is required. The transdermal route is, therefore, a better alternative, to achieve constant **plasma** level, which additionally warrants less frequent dose regime.
The present study has been selected transdermal delivery system to achieve maximum therapeutic benefit.

MATERIALS AND METHODS

Gift sample of **timolol** maleate (TM) was obtained from Cadila Antibiotics Ltd., Ahamdabad. Hydroxy propyl methylcellulose was procured from Warner Hindustan Ltd., Hyderabad. Dibutyl phthalate, ethyl cellulose, polyvinyl alcohol (PVA), HEPES buffer, procured from Sigma Chemical Co. St. Locus Mo, USA. All other chemicals and regent used were of analytical reagent grade.

Fabrication of matrix diffusion patches

Matrix patches were casted4 on mercury using stainless steel rings having inner diameter of 1.5 cm and thickness 0.5 cm were used for holding the polymer solution on mercury surface. Two type of polymer patches were prepared; HPMC and EC combination and with PVA. The polymer solutions were prepared by dissolving HPMC 10% ands EC 10 % separately in methanol- chloroform (1:1) mixture. Both solutions were mixed together in combination of 1:9, 2:8, 3:7, 4:6 and 5:5 respectively using 1% dibutyl phthalate as plasticizer. A weighed amount of drug is dispersed in polymer mixture then poured in ring placed on mercury surface in petri dish at a uniform place and solvent evaporation was controlled by conveying with funnel. After evaporation of the solvent, the film was taken out from the metal ring by sharp knife and preserve in aluminum foil. Similar procedure was adopted to prepare PVA matrix patch preparation having polymer **concentration** of 5, 10.and 15% in water with 0.5% glycerin as plasticizer.

Physical characterization

Thickness of polymeric patch was measured by using a dial gauge (Mercer, England), having least count of 0.002 mm. To maintain its shape, enough hardness is required to resist independence or penetration was determined by Hall's method4 and calculated as a functional weight. In order to determine the elongation as a tensile strength, the polymeric patch was pulled by means of a pulley system; weights were gradually added to the pan to increase the pulling force till the patch was broken. The elongation i.e. the distance traveled by the pointer before break of the patch was noted with the help of magnifying glass on the graph paper5, the tensile strength was calculated as kg/ cm2. The presence of moisture may not affect the hardness of patch in the normal environmental conditions, but it may affect in exaggerated conditions. The polymer patches were cut, weighed and placed in a humidity chamber maintained at 68% RH for 72 h for equilibrium. After 72 h polymer patch were taken out and weight accurately. The difference between initial and final weight was computed as percentage moisture absorbed. The water vapor transmission (WVT) from the film was calculated by Crowfold and Esmeric formula 6. It was determined at 25+ 20C at 68%RH. Glass weighing bottles of equal diameter (2.5 cm) and height (5.0 cm) were used as WVT cells. A weight quantity of anhydrous calcium chloride was taken up to 10 mm height in each cell and a thin layer of silicon adhesive grease applied over the brim then patch was placed on brim and adhesive was allowed to set for 5 minutes. The cells are accurately weighed and kept in humidity chamber maintained at 68% RH for 24 h. After 24 h, the cells were again weighed

and an increase in weight was considered as a quantitative measure of the moisture transmitted through the patch. Drug distribution studies: The distribution of drug in polymer patch effect the release rate. It was studied microscopically with the help of Lietz Microscope to observe uniform distribution of drug in patch.

Stability studies:

Stability studies of all patches were performed at different storage condition by measuring tensile strength, moisture content and drug content (spectrophotometric method). The measurement were carried out by keeping the patches at different conditions of temperature 280C, 350C and 500C and relative humidity of 30%, 50%, 68 % for storage period of three months at room temperature (25±10C). The patches, which maintained uniformity, shape, toughness, drug content and flexibility at all temperature and RH, were selected for further permeation studies.

Skin Preparation:

The full thickness human cadaver skin was washed with purified water after removal of all subcutaneous fat and hairs and cut in to pieces for experimental use. The skin pieces were soaked in HEPES buffer and store in freezer at 300C until used. Just before the experiment, it was thawed at room temperature and checked for any microscopical damage.

In vitro drug permeation studies:

A drug permeation study was carried out with drug solution in HEPES buffer pH7.4 and stable patches through human cadaver skin using modified kieshry- chein diffusion cells. The **concentration** of drug kept similar in drug solution in HEPES buffer and patches to compare permeation profile. The Patches and drug solution were kept on stratum cornium side of cells and this patch - skin - complex sandwiched between donor and receptor compartment. The receiving compartment contains blank 10.0 ml of HEPES buffer pH 7.4 and touches the dermal side of the skin. The whole of the assembly was kept on magnetic stirrer, which thermostatically controlled at 37+ 2oC at 100 rpm. Samples were withdrawn at pre set time interval from the receiving compartment and analyzed spectrophotometrically at 294 nm using shimadzu-1601 UV- visible spectrophotometer. The fresh buffer in receiving compartment was replaced after each withdrawal. The permeation studies determined for period of 4 h. and calculated as cumulative percent drug permeated.

Results

In present studies, the polymer and plasticizer choice for patch preparation were based on no interaction with drug and HEPES buffer with considerable stability. Various combinations of polymers hydroxy propyl methyl cellulose (HPMC) and ethyl cellulose (EC) and various

concentration of polyvinyl alcohol were tried for patch preparation and evaluated for physical studies (Table 1).

Formulation Code	Polymer Used	Polymer Core % w/v	Thickness Mm	Hardness Gm/cm	Tensile strength Kg/cm2	WVT gm/cm2 / 4 h	Moisture absorption %
HE1	HPMC:EC	1:9	0.034	322	2.12	2.20	2.11
HE2	HPMC:EC	2:8	0.036	314	2.98	2.63	2.43
HE3	HPMC:EC	3:7	0.035	312	3.00	2.98	2.88
HE4	HPMC:EC	4:6	0.035	306	3.51	3.23	3.03
HE5	HPMC:EC	5:5	0.033	302	3.83	3.40	3.1
P5	PVA	5.0	0.031	290	2.00	3.02	2.99
P10	PVA	10	0.036	298	2.10	0.32	3.22
P15	PVA	15	0.034	302	2.54	4.01	4.00

Table 1: Physical evaluation of polymeric patch of Timilol maleate

The main physical evaluations considered for stability were WVT rate, tensile strength and % moisture absorption and drug content. The polymer patch prepared with combination in the ratio of 2:8 HPMC and EC (HE2), PVA of 10% w/v (P10) were found to be satisfactory at all temperatures and relative humidity. On the basis of physical and stability studies, the patches HE2 and PVA10 were considered for permeation studies. The in- vitro permeation studies of drug solution and patches were performed to observe permeation profile. The permeation profile of both solution and patches were compared

Discussion

The in- vitro stability studies of all patches were performed in terms of stability against storage conditions and aging effect, because TM is a drug used for long therapy to maintain its therapeutic effect especially when used as antihypertensive agent. The physical characterization like tensile strength, moisture absorption and WVT rate and drug content were main parameter for stability studies, which revealed no appreciable changes occurred in patches (HE2 & PVA10) at normal storage conditions (250C+1). The drug solution permeation profile suggests that it followed Fick's law of diffusion. Linear relationship between cumulative percent drug permeated verses time indicate zero order permeation of drug through human cadaver skin with lag time 35 minutes. The transdermal permeability coefficient of TM was calculated to be 323x10-5 +0.02cm2/h from the steady state portion of the curve (Fig.1).

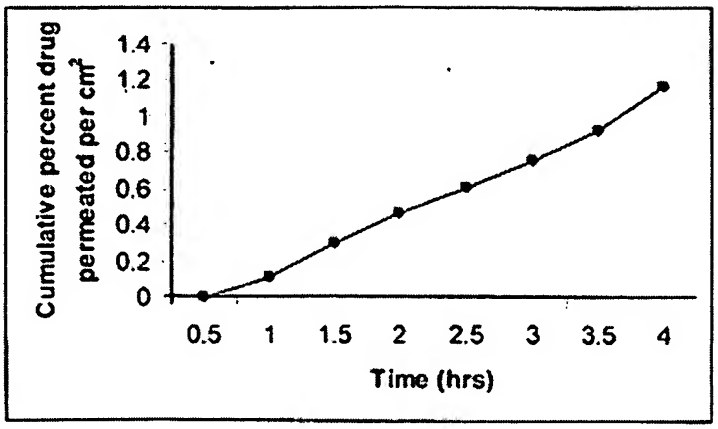

Fig.1: In-vitro permeation profile of timolol maleate from drug solution through human cadaver skin.

The permeation profile of drug from both patches HE2 and PVA10 when plotted,between permeation data against square root of time shows linear relationship indicating drug permeation followed Higuhi equation (Fig.2).

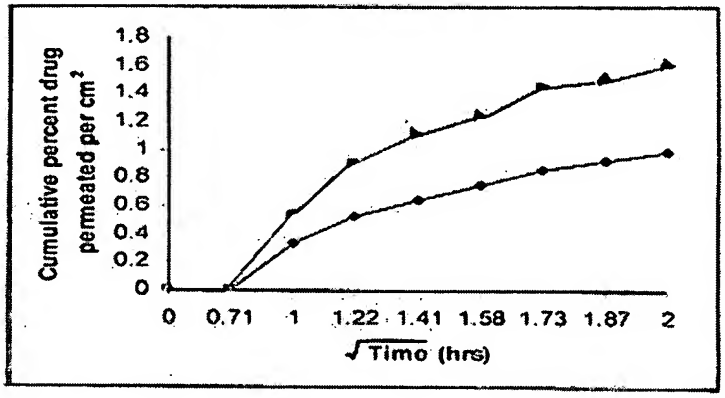

Fig.2 : In-vitro permeation profiles of timolol maleate from selected matrix diffusion patches through human cadaver skin. HE_2 (■), PVA_{10} (▲).

The permeation profile data of patches were plotted in log values with time, the slope value comes near to 0.49+0.01SD (~ 0.5), suggesting drug permeation is controlled by diffusion within the matrix rather than by skin.
When we compare both patches, the PVA10 system provide higher 1.589 + 0.20 SD % drug/ cm2 of permeation rather than HE2, i.e., 0.987 +0.20 % drug/ cm2 in 4h of period.

Conclusion

The studies suggest that both reservoir as well as matrix system of transdermal delivery of TM is possible. The reservoir system followed zero order while the matrix system followed first order release profile. Among both matrix systems PVA10 patch have more permeability than HE2 patch.

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Note: Performing your original search, ***half life timolol***, in PubMed will retrieve *38* citations.

1: Br J Clin Pharmacol. 1997 Mar;43(3):301-8. Related Articles, Links

A prospective study of the effects of prolonged timolol therapy on alpha- and beta-adrenoceptor and angiotensin II receptor mediated responses in normal subjects.

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Clinical Pharmacology Unit, University of Cambridge, Addenbrooke's Hospital.

AIMS: Long-term treatment with beta 1-selective adrenergic antagonists gives rise to cross-sensitisation of cardiac beta 2-adrenoceptor responses, with no corresponding alteration in beta 1-adrenoceptor responses. We performed a prospective randomised double-blind placebo-controlled cross-over study of the effects of nonselective beta-blockade with timolol on alpha-adrenergic and angiotensin II receptor mediated responses in normal subjects. We also wished to study the time course of beta 1- and beta 2-adrenergic responses after withdrawal of timolol. METHODS: Six healthy males received timolol 10 mg twice daily or placebo for 14 days. On day 11 of treatment, vascular alpha 1-, alpha 2- and angiotensin II receptor responses were assessed by measuring the blood pressure increases in response to intravenous phenylephrine, alpha-methylnoradrenaline and angiotensin amide respectively, following one dose of timolol 10 mg (to block the beta-adrenergic effects of phenylephrine and alpha-methylnoradrenaline). Both systolic and diastolic blood pressure increased in response to each of these drugs, but these increases were not different on timolol treatment or placebo. Following cessation of treatment with timolol or placebo, beta 1- and beta 2-adrenoceptor mediated responses were assessed by measuring the heart rate responses to treadmill exercise and intravenous salbutamol infusion respectively. Half each of the subjects underwent this 2 days and 3 days respectively, after the end of treatment. RESULTS: Both exercise-induced and salbutamol-induced tachycardia were not different following placebo or 3 days following the end of timolol treatment. However, 2 days following timolol treatment, both were attenuated; the reduction in salbutamol-induced tachycardia was significant, whilst the reduction in exercise tachycardia did not reach statistical significance. We also measured metabolic responses to exercise and to salbutamol infusion. Exercise induced a rise in plasma potassium and noradrenaline. Salbutamol produced a fall in plasma potassium, a rise in plasma glucose and insulin and also a rise in plasma noradrenaline. All of these changes were not different following placebo or 3 days after the end of timolol treatment; by contrast, 2 days following timolol treatment, all were significantly attenuated, with the

exception of the rise in plasma glucose. In addition, the rise in both plasma glucose and insulin in response to an oral load of 75 g glucose were not different post-placebo, 2 or 3 days post-timolol. CONCLUSIONS: These results show that, following 14 days of nonselective beta-adrenoceptor blockade with timolol, there is evidence of residual beta-adrenoceptor blockade 2 days after drug withdrawal; this finding is in contrast with the known plasma profile of timolol (half-life 3-6 hours), but is consistent with our previous observations of the slow speeds of association and dissociation of timolol with beta-adrenoceptors in vitro. There is no evidence, in this study, of beta-adrenergic sensitisation following timolol withdrawal, nor of cross-regulation of vascular alpha 1-, alpha 2- or angiotensin II receptors in response to nonselective beta-adrenoceptor blockade.

Publication Types:

- Clinical Trial
- Randomized Controlled Trial

PMID: 9088585 [PubMed - indexed for MEDLINE]

DrugBank
Timolol
(APRD00229)

Show Similar Structure(s) for Approved Drugs

Creation Date	2005/6/27 6:31:0 GMT
Last Update	Mar 30, 2006
Accession Number	APRD00229
Generic Name	**Timolol**
Brand Names/Synonyms	1. Apo-Timol 2. Apo-Timop 3. Aquanil 4. Betim 5. Betimol 6. Blocadren 7. Istalol 8. Novo-Timol 9. Proflax 10. Temserin 11. Tenopt 12. Tim-AK 13. Timacar 14. Timacor 15. Timololum [INN-Latin] 16. Timopic

	17. Timoptic 18. Timoptic in Ocudose 19. Timoptic-XE 20. Timoptol
Brand Name Mixtures	1. Combigan (Brimonidine Tartrate + **Timolol** Maleate) 2. Cosopt -(2%/0.5% Oph Dps) (Dorzolamide Hydrochloride + **Timolol** Maleate) 3. Timolide Tab (Hydrochlorothiazide + **Timolol** Maleate) 4. Timpilo 2 (Pilocarpine Hydrochloride + **Timolol** Maleate) 5. Timpilo 4 (Pilocarpine Hydrochloride + **Timolol** Maleate) 6. Xalacom (Latanoprost + **Timolol** Maleate)
Chemical IUPAC Name	1-[(4-morpholin-4-yl-1,2,5-thiadiazol-3-yl)oxy]-3-tert-butylamino-propan-2-ol
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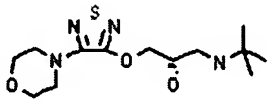
Chemical Structure	
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InChi Identifier	InChI=1/C13H24N4O3S/c1-13(2,3)14-8-10(18)9-20-12-11(15-21-16-12)17-4-6-19-7-5-17/h10,14,18H,4-9H2,1-3H3/t10-/m0/s1
KEGG Compound ID	C07141
PubChem ID	SID:175467
ChEBI ID	Not Available
PharmGKB ID	PA451690
HET ID	Not Available
SwissProt ID	Not Available
GenBank ID	Not Available
Drug ID Number [DIN]	00812455
RxList Link	**Timolol**
FDA Label	Click for FDA Label (pdf)
Material Safety Data Sheet (MSDS)	Click Here for MSDS File (pdf)
Synthesis Reference	Wasson et al., J. Med. Chem. 15, 615 (1972)
Molecular Weight	316.421 g/mol

Melting Point	201.5-202.5 °C
H_2O Solubility	2.74 mg/mL
State	Solid
LogP/Hydrophobicity	1.761
pKa/Isoelectric Point	3.9
NMR Spectrum	Not Available
Mass Spectrum	Not Available
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SDF File	Click Here for SDF File
PDB File Calculated Image	View 3D Structure
PDB File Calculated Text	Click Here for PDB File
PDB Experimental ID	Not Available
Smiles String	CC(C)(C)NCC(COC1=NSN=C1N2CCOCC2)O
Drug Type	Approved Drug
Drug Category	▪ Antihypertensive Agents ▪ Anti-Arrhythmia Agents ▪ Adrenergic beta-Antagonists ▪ ATC:C07AA06 ▪ ATC:S01ED01
Indication	In its oral form it is used to treat high blood pressure and prevent heart attacks, and occasionally to prevent migraine headaches. In its opthalmic form it is used to treat open-angle and occasionally secondary glaucoma.
Pharmacology	Similar to propranolol and nadolol, **timolol** is a non-selective, beta-adrenergic receptor antagonist. **Timolol** does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anesthetic (membrane-stabilizing) activity, but does possess a relative high degree of lipid solubility. **Timolol**, when applied topically to the eye, has the action of reducing elevated, as well as normal, intraocular pressure, whether or not accompanied by glaucoma. Elevated intraocular pressure is a major risk factor in the pathogenesis of glaucomatous visual field loss and optic nerve damage.
Mechanism of Action	Like propranolol and nadolol, **timolol** competes with adrenergic neurotransmitters such as catecholamines for binding at beta(1)-adrenergic receptors in the heart and vascular smoo muscle and beta(2)-receptors in the bronchial and vascular smooth muscle. Beta(1)-recept blockade results in a decrease in resting and exercise heart rate and cardiac output, a decrease in both systolic and diastolic blood pressure, and, possibly, a reduction in reflex orthostatic hypotension. Beta(2)-blockade results in an increase in peripheral vascular resistance. The exact mechanism whereby **timolol** reduces ocular pressure is still not kno The most likely action is by decreasing the secretion of aqueous humor.

Absorption	Bioavailability is about 60%
Toxicity	LD_{50}=1190 mg/kg (oral, mice), LD_{50}=900 mg/kg (oral, rat). Symptoms of overdose include drowsiness, vertigo, headache, and atriventricular block.
Protein Binding	~10%
Biotransformation	Primarily hepatic (80%) via the cytochrome P450 2D6 isoenzyme.
Half Life	2.5-5 hours
Dosage Forms	▪ Drops ▪ Liquid ▪ Solution ▪ Solution (long-acting) ▪ Tablet
Patient Information	Click for Patient Information
Interactions	Click for Interactions
Contraindications	Click for Contraindications
Drug Reference	http://www.drugs.com/cons/**Timolol**.html http://www.rxlist.com/cgi/generic3/timololgfs.htm http://www.inchem.org/documents/pims/pharm/**timolol**.htm
Phase 1 Metabolizing Enzyme	CYP2D6
Phase 1 Metabolizing Enzyme Sequence	> sp|P10635|CP2D6_HUMAN Cytochrome P450 2D6 MGLEALVPLAVIVAIFLLLVDLMHRRQRWAARYPPGPLPLPGLGNLLHVDFQNTPYCFDQ LRRRFGDVFSLQLAWTPVVVLNGLAAVREALVTHGEDTADRPPVPITQILGFGPRSQGVF LARYGPAWREQRRFSVSTLRNLGLGKKSLEQWVTEEAACLCAAFANHSGRPFRPNGLLDK AVSNVIASLTCGRRFEYDDPRFLRLLDLAQEGLKEESGFLREVLNAVPVLLHIPALAGKV LRFQKAFLTQLDELLTEHRMTWDPAQPPRDLTEAFLAEMEKAKGNPESSFNDENLRIVVA DLFSAGMVTTSTTLAWGLLLMILHPDVQRRVQQEIDDVIGQVRRPEMGDQAHMPYTTAVI HEVQRFGDIVPLGMTHMTSRDIEVQGFRIPKGTTLITNLSSVLKDEAVWEKPFRFHPEHF LDAQGHFVKPEAFLPFSAGRRACLGEPLARMELFLFFTSLLQHFSFSVPTGQPRPSHHGV FAFLVSPSPYELCAVPR
Phase 1 Metabolizing Enzyme SwissProt ID	CP2D6_HUMAN

Drug Target 1

Drug Target 1 Name	Beta-1 Adrenergic Receptor
Drug Target 1 Gene Name	ADRB1
Drug Target 1 Synonyms	1. Beta-1 adrenergic receptor 2. Beta-1 adrenoceptor 3. Beta-1 adrenoreceptor
Drug Target 1 Protein Sequence	> Beta-1 Adrenergic Receptor MGAGVLVLGASEPGNLSSAAPLPDGAATAARLLVPASPPASLLPPASESPEPLSQQWTAG MGLLMALIVLLIVAGNVLVIVAIAKTPRLQTLTNLFIMSLASADLVMGLLVVPFGATIVV WGRWEYGSFFCELWTSVDVLCVTASIETLCVIALDRYLAITSPFRYQSLLTRARARGLVC TVWAISALVSFLPILMHWWRAESDEARRCYNDPKCCDFVTNRAYAIASSVVSFYVPLCIM

	AFVYLRVFREAQKQVKKIDSCERRFLGGPARPPSPSPSPVPAPAPPPGPPRPAAAAATAP LANGRAGKRRPSRLVALREQKALKTLGIIMGVFTLCWLPFFLANVVKAFHRELVPDRLFV FFNWLGYANSAFNPIIYCRSPDFRKAFQRLLCCARRAARRRHATHGDRPRASGCLARPGP PPSPGAASDDDDDDVVGATPPARLLEPWAGCNGGAAADSDSSLDEPCRPGFASESKV
Drug Target 1 Number of Residues	477
Drug Target 1 Molecular Weight	51323 g/mol
Drug Target 1 Theoretical pI	9.03
Drug Target 1 GO Classification	>>> Function: signal transducer activity Function: receptor activity Function: transmembrane receptor activity Function: G-protein coupled receptor activity Function: rhodopsin-like receptor activity Function: amine receptor activity Function: adrenoceptor activity Function: beta-adrenergic receptor activity Function: beta1-adrenergic receptor activity || >>> Process: cellular process Process: cell communication Process: signal transduction Process: cell surface receptor linked signal transduction Process: G-protein coupled receptor protein signaling pathway || >>> Component: cell Component: membrane Component: integral to membrane
Drug Target 1 General Function	Receptor activity and cell communication
Drug Target 1 Specific Function	Beta-adrenergic receptors mediate the catecholamine- induced activation of adenylate cyclase through the action of G proteins. This receptor binds epinephrine and norepinephri with approximatively equal affinity
Drug Target 1 Pathway	Not Available
Drug Target 1 Reaction	Not Available
Drug Target 1 Pfam Domain Function	PF00001 7tm_1
Drug Target 1 Signals	None
Drug Target 1 Transmembrane Regions	60-83 97-120 132-155 176-199

	222-245 326-349 357-380
Drug Target 1 Essentiality	Not Available
Drug Target 1 GenBank ID Protein	178200
Drug Target 1 SwissProt ID	ADRB1_HUMAN (P08588)
Drug Target 1 PDB ID	Not Available
Drug Target 1 3D Structure Text	Not Available
Drug Target 1 3D Structure Image	Not Available
Drug Target 1 Cellular Location	Integral membrane protein
Drug Target 1 Gene Sequence	> Beta-1 Adrenergic Receptor, 1434 bp ATGGGCGCGGGGGTGCTCGTCCTGGGCGCCTCCGAGCCCGGTAACCTGTCGTCGGCCGCA CCGCTCCCCGACGGCGCGGCCACCGCGGCGCGGCTGCTGGTGCCCGCGTCGCCGCCCGCC TCGTTGCTGCCTCCCGCCAGCGAAAGCCCCGAGCCGCTGTCTCAGCAGTGGACAGCGGGC ATGGGTCTGCTGATGGCGCTCATCGTGCTGCTCATCGTGGCGGGCAATGTGCTGGTGATC GTGGCCATCGCCAAGACGCCGCGGCTGCAGACGCTCACCAACCTCTTCATCATGTCCCTG GCCAGCGCCGACCTGGTCATGGGGCTGCTGGTGGTGCCGTTCGGGGCCACCATCGTGGTG TGGGGCCGCTGGGAGTACGGCTCCTTCTTCTGCGAGCTGTGGACCTCAGTGGACGTGCTG TGCGTGACGGCCAGCATCGAGACCCTGTGTGTCATTGCCCTGGACCGCTACCTCGCCATC ACCTCGCCCTTCCGCTACCAGAGCCTGCTGACGCGCGCGCGGGCGCGGGGCCTCGTGTGC ACCGTGTGGGCCATCTCGGCCCTGGTGTCCTTCCTGCCCATCCTCATGCACTGGTGGCGG GCGGAGAGCGACGAGGCGCGCCGCTGCTACAACGACCCCAAGTGCTGCGACTTCGTCACC AACCGGGCCTACGCCATCGCCTCGTCCGTAGTCTCCTTCTACGTGCCCCTGTGCATCATG GCCTTCGTGTACCTGCGGGTGTTCCGCGAGGCCCAGAAGCAGGTGAAGAAGATCGACAGC TGCGAGCGCCGTTTCCTCGGCGGCCCAGCGCGGCCGCCCTCGCCCTCGCCCTCGCCCGTC CCCGCGCCCGCGCCGCCGCCCGGACCCCCGCGCCCCGCCGCCGCCGCCGCCACCGCCCCG CTGGCCAACGGGCGTGCGGGTAAGCGGCGGCCCTCGCGCCTCGTGGCCCTACGCGAGCAG AAGGCGCTCAAGACGCTGGGCATCATCATGGGCGTCTTCACGCTCTGCTGGCTGCCCTTC TTCCTGGCCAACGTGGTGAAGGCCTTCCACCGCGAGCTGGTGCCCGACCGCCTCTTCGTC TTCTTCAACTGGCTGGGCTACGCCAACTCGGCCTTCAACCCCATCATCTACTGCCGCAGC CCCGACTTCCGCAAGGCCTTCCAGGGACTGCTCTGCTGCGCGCGCAGGGCTGCCCGCCGG CGCCACGCGACCCACGGAGACCGGCCGCGCGCCTCGGGCTGTCTGGCCCGGCCCGGACCC CCGCCATCGCCCGGGGCCGCCTCGGACGACGACGACGACGATGTCGTCGGGGCCACGCCG CCCGCGCGCCTGCTGGAGCCCTGGGCCGGCTGCAACGGCGGGGCGGCGGCGGACAGCGAC TCGAGCCTGGACGAGCCGTGCCGCCCCGGCTTCGCCTCGGAATCCAAGGTGTAG
Drug Target 1 GenBank ID Gene	J03019
Drug Target 1 Chromosome Location	Chromosome:10
Drug Target 1 Locus	10q24-q26

	refSNP ID	Function Validation	Alleles Position	Amino Acids Position	Allele Frequencies
					African: A 0.992 G 0.008

Drug Target 1 SNPs	rs1801252	nonsynonymous [2+4+5]	A-G 256	Not Available	European: Not Available Asian: A 1 G 0
	rs1801253	nonsynonymous [2+4+5]	C-G 256	Not Available	African: G 0.408 C 0.592 European: G 0.317 C 0.683 Asian: G 0.2 C 0.8
	rs180897	nonsynonymous 5	C-T 201	Not Available	African: C 1 T 0 European: C 1 T 0 Asian: C 1 T 0
Drug Target 1 References	2825170 10477438 10212248 11052857 11854867				

Drug Target 2

Drug Target 2 Name	Beta-2 Adrenergic Receptor
Drug Target 2 Gene Name	ADRB2
Drug Target 2 Synonyms	1. Beta-2 adrenergic receptor 2. Beta-2 adrenoceptor 3. Beta-2 adrenoreceptor
Drug Target 2 Protein Sequence	> Beta-2 Adrenergic Receptor MGQPGNGSAFLLAPNRSHAPDHDVTQQRDEVWVVGMGIVMSLIVLAIVFGNVLVITAIAK FERLQTVTNYFITSLACADLVMGLAVVPFGAAHILMKMWTFGNFWCEFWTSIDVLCVTAS IETLCVIAVDRYFAITSPFKYQSLLTKNKARVIILMVWIVSGLTSFLPIQMHWYRATHQE AINCYANETCCDFFTNQAYAIASSIVSFYVPLVIMVFVYSRVFQEAKRQLQKIDKSEGRF HVQNLSQVEQDGRTGHGLRRSSKFCLKEHKALKTLGIIMGTFTLCWLPFFIVNIVHVIQD NLIRKEVYILLNWIGYVNSGFNPLIYCRSPDFRIAFQELLCLRRSSLKAYGNGYSSNGNT GEQSGYHVEQEKENKLLCEDLPGTEDFVGHQGTVPSDNIDSQGRNCSTNDSLL
Drug Target 2 Number of Residues	413
Drug Target 2 Molecular Weight	46557 g/mol
Drug Target 2 Theoretical pI	7.44
Drug Target 2 GO Classification	>>> Function: signal transducer activity Function: receptor activity Function: transmembrane receptor activity Function: G-protein coupled receptor activity Function: rhodopsin-like receptor activity Function: amine receptor activity Function: adrenoceptor activity Function: beta-adrenergic receptor activity Function: beta2-adrenergic receptor activity || >>> Process: cellular process

	Process: cell communication Process: signal transduction Process: cell surface receptor linked signal transduction Process: G-protein coupled receptor protein signaling pathway || >>> Component: cell Component: membrane Component: integral to membrane
Drug Target 2 General Function	Receptor activity and cell communication
Drug Target 2 Specific Function	Beta-adrenergic receptors mediate the catecholamine- induced activation of adenylate cyclase through the action of G proteins. The beta-2-adrenergic receptor binds epinephrine with an approximately 30-fold greater affinity than it does norepinephrine
Drug Target 2 Pathway	Not Available
Drug Target 2 Reaction	Not Available
Drug Target 2 Pfam Domain Function	PF00001 7tm_1
Drug Target 2 Signals	None
Drug Target 2 Transmembrane Regions	35-58 72-95 107-129 151-174 197-220 275-298 306-329
Drug Target 2 Essentiality	Not Available
Drug Target 2 GenBank ID Protein	29371
Drug Target 2 SwissProt ID	ADRB2_HUMAN (P07550)
Drug Target 2 PDB ID	Not Available
Drug Target 2 3D Structure Text	Not Available
Drug Target 2 3D Structure Image	Not Available
Drug Target 2 Cellular Location	Integral membrane protein
	> Beta-2 Adrenergic Receptor, 1242 bp ATGGGGCAACCCGGGAACGGCAGCGCCTTCTTGCTGGCACCCAATAGAAGCCATGCGCCG GACCACGACGTCACGCAGCAAAGGGACGAGGTGTGGGTGGTGGGCATGGGCATCGTCATG TCTCTCATCGTCCTGGCCATCGTGTTTGGCAATGTGCTGGTCATCACAGCCATTGCCAAG TTCGAGCGTCTGCAGACGGTCACCAACTACTTCATCACTTCACTGGCCTGTGCTGATCTG

Drug Target 2 Gene Sequence	GTCATGGGCCTGGCAGTGGTGCCCTTTGGGGCCGCCCATATTCTTATGAAAATGTGGACT TTTGGCAACTTCTGGTGCGAGTTTTGGACTTCCATTGATGTGCTGTGCGTCACGGCCAGC ATTGAGACCCTGTGCGTGATCGCAGTGGATCGCTACTTTGCCATTACTTCACCTTTCAAG TACCAGAGCCTGCTGACCAAGAATAAGGCCCGGGTGATCATTCTGATGGTGTGGATTGTG TCAGGCCTTACCTCCTTCTTGCCCATTCAGATGCACTGGTACCGGGCCACCCACCAGGAA GCCATCAACTGCTATGCCAATGAGACCTGCTGTGACTTCTTCACGAACCAAGCCTATGCC ATTGCCTCTTCCATCGTGTCCTTCTACGTTCCCCTGGTGATCATGGTCTTCGTCTACTCC AGGGTCTTTCAGGAGGCCAAAAGGCAGCTCCAGAAGATTGACAAATCTGAGGGCCGCTTC CATGTCCAGAACCTTAGCCAGGTGGAGCAGGATGGGCGGACGGGGCATGGACTCCGCAGA TCTTCCAAGTTCTGCTTGAAGGAGCACAAAGCCCTCAAGACGTTAGGCATCATCATGGGC ACTTTCACCCTCTGCTGGCTGCCCTTCTTCATCGTTAACATTGTGCATGTGATCCAGGAT AACCTCATCCGTAAGGAAGTTTACATCCTCCTAAATTGGATAGGCTATGTCAATTCTGGT TTCAATCCCCTTATCTACTGCCGGAGCCCAGATTTCAGGATTGCCTTCCAGGAGCTTCTG TGCCTGCGCAGGTCTTCTTTGAAGGCCTATGGGAATGGCTACTCCAGCAACGGCAACACA GGGGAGCAGAGTGGATATCACGTGGAACAGGAGAAAGAAAATAAACTGCTGTGTGAAGAC CTCCCAGGCACGGAAGACTTTGTGGGCCATCAAGGTACTGTGCCTAGCGATAACATTGAT TCACAAGGGAGGAATTGTAGTACAAATGACTCACTGCTGTAA
Drug Target 2 GenBank ID Gene	Y00106
Drug Target 2 Chromosome Location	Chromosome:5
Drug Target 2 Locus	5q31-q32

Drug Target 2 SNPs

refSNP ID	Function / Validation	Alleles / Position	Amino Acids / Position	Allele Frequencies
rs1042714	nonsynonymous [1+2+4+5]	C-G 329	Glu[E]-Gln[Q] 27	African: G 0.175 C 0.825 European: G 0.467 C 0.533 Asian: G 0.101 C 0.899
rs1042713	nonsynonymous [2+4+5]	A-G 296	Gly[G]-Arg[R] 16	African: G 0.525 A 0.475 European: G 0.675 A 0.325 Asian: G 0.539 A 0.461
rs1800888	nonsynonymous [1+2+5]	C-T 741	Ile[I]-Thr[T] 164	African: C 1 T 0 European: C 0.992 T 0.008 Asian: C 1 T 0
rs1042718	synonymous [1+2+4+5]	A-C 773	Arg[R]-Gly[G] 175	African: C 0.65 A 0.35 European: C 0.808 A 0.192 Asian: C 0.568 A 0.432
rs1042717	synonymous [1+2+4]	A-G 502	Leu[L]-Leu[L] 84	Not Available
rs1042720	synonymous [1+4]	A-G/T 201	Leu[L]-Leu[L] 413	Not Available
rs1042719	synonymous [1+2]	C-G 1303	Gly[G]-Gly[G] 351	African: G 0.643 C 0.357 European: Not Available Asian: G 0.477 C 0.523
rs3730182	synonymous [1]	C-T 102	Thr[T]-Thr[T] 393	Not Available
rs1801704	untranslated	C-T	Not Available	African: C 0.138 T 0.862 European: Not Available

		[1+2+4]	231		Asian: C 0.048 T 0.952
	rs1042711	untranslated	C-T	Not Available	African: C 0.123 T 0.877 European: Not Available Asian: C 0.054 T 0.946
		[1+2+4]	204		
	rs3729943	nonsynonymous	C-G	Cys[C]-Ser[S]	Not Available
		5	151	220	
	rs3729944	synonymous	C-T	His[H]-His[H]	African: T 1 C 0 European: T 1 C 0 Asian: T 1 C 0
		5	151	390	
Drug Target 2 References	3033609 3025863 3026848 2823249 3034889 2831218 2540197 11146000 8383511 7915137 7706471				
Organisms Affected	Humans and other mammals				

Contact: **David Wishart** (Last Update: Mar 30, 2006)

CLINICAL PHARMACOLOGY

Mechanism of Action

COSOPT*(Dorzolamide/**Timolol** Maleate) is comprised of two components: dorzolamide hydrochloride and **timolol** maleate. Each of these two components decreases elevated intraocular pressure, whether or not associated with glaucoma, by reducing aqueous humor secretion. Elevated intraocular pressure is a major risk factor in the pathogenesis of optic nerve damage and glaucomatous visual field loss. The higher the level of intraocular pressure, the greater the likelihood of glaucomatous field loss and optic nerve damage.

Dorzolamide hydrochloride is an inhibitor of human carbonic anhydrase II. Inhibition of carbonic anhydrase in the ciliary processes of the eye decreases aqueous humor

secretion, presumably by slowing the formation of bicarbonate ions with subsequent reduction in sodium and fluid transport. **Timolol** maleate is a beta$_1$ and beta$_2$ (non-selective) adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anesthetic (membrane-stabilizing) activity. The combined effect of these two agents administered as COSOPT b.i.d. results in additional intraocular pressure reduction compared to either component administered alone, but the reduction is not as much as when dorzolamide t.i.d. and **timolol** b.i.d. are administered concomitantly (see **Clinical Studies** below).

Pharmacokinetics/Pharmacodynamics

Dorzolamide Hydrochloride

When topically applied, dorzolamide reaches the systemic circulation. To assess the potential for systemic carbonic anhydrase inhibition following topical administration, drug and metabolite concentrations in RBCs and **plasma** and carbonic anhydrase inhibition in RBCs were measured. Dorzolamide accumulates in RBCs during chronic dosing as a result of binding to CA-II. The parent drug forms a single N-desethyl metabolite, which inhibits CA-II less potently than the parent drug but also inhibits CA-I. The metabolite also accumulates in RBCs where it binds primarily to CA-I. **Plasma** concentrations of dorzolamide and metabolite are generally below the assay limit of quantitation (15nM). Dorzolamide binds moderately to **plasma** proteins (approximately 33%).

Dorzolamide is primarily excreted unchanged in the urine; the metabolite also is excreted in urine. After dosing is stopped, dorzolamide washes out of RBCs nonlinearly, resulting in a rapid decline of drug **concentration** initially, followed by a slower elimination phase with a half-life of about four months.

To simulate the systemic exposure after long-term topical ocular administration, dorzolamide was given orally to eight healthy subjects for up to 20 weeks. The oral dose of 2 mg b.i.d. closely approximates the amount of drug delivered by topical ocular administration of dorzolamide 2% t.i.d. Steady state was reached within 8 weeks. The inhibition of CA-II and total carbonic anhydrase activities was below the degree of inhibition anticipated to be necessary for a pharmacological effect on renal function and respiration in healthy individuals.

Timolol Maleate

In a study of **plasma** drug concentrations in six subjects, the systemic exposure to **timolol** was determined following twice daily topical administration of **timolol** maleate ophthalmic solution 0.5%. The mean **peak plasma concentration** following morning dosing was 0.46 ng/mL.

Clinical Studies

Clinical studies of 3 to 15 months duration were conducted to compare the IOP-lowering effect over the course of the day of COSOPT b.i.d. (dosed morning and bedtime) to individually- and concomitantly-administered 0.5% **timolol** (b.i.d.) and 2.0% dorzolamide (b.i.d. and t.i.d.). The IOP-lowering effect of COSOPT b.i.d. was greater (1-3 mmHg) than that of monotherapy with either 2.0% dorzolamide t.i.d. or 0.5% **timolol** b.i.d. The IOP-lowering effect of COSOPT b.i.d. was approximately 1 mmHg less than that of concomitant therapy with 2.0% dorzolamide t.i.d. and 0.5% **timolol** b.i.d.

Open-label extensions of two studies were conducted for up to 12 months. During this period, the IOP-lowering effect of COSOPT b.i.d. was consistent during the 12 month follow-up period.

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Timolo

13. REFERENCES

14. AUTHOR(S), REVIEWER(S), DATE(S) (INCLUDING UPDATES), COMPLETE ADDRESS(ES)

PHARMACEUTICALS

1. NAME

1.1 Substance

Timolol

1.2 Group

beta-blocker; adrenergic beta-receptor blocking agent, Class II antiarrhythmic drug

1.3 Synonyms

Timolol maleate

MK-950

(-)-3-morpholino-4-(3-tert-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole

1.4 Identification numbers

1.4.1 CAS number

26839-75-8

1.4.2 Other numbers

Timolol maleate : 26921-17-5

1.5 Brand names, Trade names

Betim (Denmark; Netherlands; Leo, Norway; Lovens, Sweden; Leo, UK; Belgim); Blocadren (Frosst, Australia; Belgium; Frosst, Canada; Merck Sharp & Dohme, Italy; Netherlands; Merck Sharp & Dohme, Norway; Merck Sharp & Dohme, South Africa; Spain ; MSD, Sweden; MSD Switzerland; MSD, UK; MSD, USA); Blocanol (Finland); Chibro-Timoptol (Germany); Cusimolol (Cusi, Spain); Oftan-**Timolol** (NAF, Norway); Proflax (Merck Sharp & Dohme, Argentina); Temserin (Frosst, Germany; Greece); Tenopt (Sigma, Australia); Tiloptic (Israel); Timacor (Denmark; Merck Sharp & Dohme-Chibret, France); Timolide (USA); **Timolol** (UK); Timoptic (Merck Sharp & Dohme, Canada; Chibret, Switzerland; Merck Sharp & Dohme, USA; Austria); Timoptol (Frosst, Australia; Merck Sharp & Dohme-Chibret, France; Chibret, Germany; Merck Sharp & Dohme, Italy; Netherlands; New Zealand; South Africa; Merck Sharp & Dohme, UK, Belgium).

1.6 Manufacturers, Importers

2. SUMMARY

2.1 Main risks and target organs

Beta-blocking agents exert their effects by competing with endogenous and/or exogenous beta-adrenergic agonists. **Timolol** is a non-cardioselective beta-blocker (it has similar affinity for $beta_1$ and $beta_2$ receptors) and it has no intrinsic sympathomimetic or membrane stabilising effect. The main risks might be an impairment of atrioventricular conduction and a negative inotropic effect (Critchley and Ungar, 1989; Frishman, 1981)

2.2 Summary of clinical effects

Only one case of acute poisoning after ingestion of 300 mg **timolol** in a 24 year-old man has been reported. The patient showed moderate toxic symptoms: drowsiness, vertigo, headache, and first degree atrioventricular block which was treated with atropine 1 mg and isoproterenol 5 mg. The patient recovered without sequelae (Tisserand, 1982).

Adverse systemic effects have been reported in patients treated with **timolol** eye drops.

2.3 Diagnosis

Symptoms are those anticipated from beta-blockade and include heart block, drowsiness, headache and vertigo.There is,

however, little reported experience of ovedose with **timolol**.

Timolol may be measured in **plasma** but **plasma** concentrations are not known to be useful for the clinical management of the patient.

2.4 First aid measures and management principles

Patients with poisoning by ingestion of **timolol** should be monitored closely, preferably in an intensive care unit.

Monitor vital signs: ECG, blood pressure, respiration.

Treatment may include:

emesis, gastric lavage, oral activated charcoal

atropine for symptomatic bradycardia, isoproterenol and/or glucagon for atrioventricular block or hypotension

3. PHYSICO-CHEMICAL PROPERTIES

3.1 Origin of the substance

Synthetic

3.2 Chemical structure

$C_{13}H_{24}N_4O_3S$

Molecular weight: 316.42

3.3 Physical properties

3.3.1 Properties of the substance

White, odourless powder.
Melting point: 201.5-202.5 °C.
Soluble 1 in 15 of water, 1 in 21 of alcohol, and 1 in 40 of chloroform; soluble in methanol; practically insoluble in ether.
A 2% solution in water has a pH of 3.8 to 4.3.
Ophthalmic preparations have a pH of 6.5 to 7.5.

(Reynolds, 1989; Merck Index, 1983)

3.3.2 Properties of the locally available formulation

See section 3.3.1.

3.4 Other characteristics

3.4.1 Shelf-life of the substance

No data available.

3.4.2 Shelf-life of the locally available formulation

No data available.

3.4.3 Storage conditions

Store in well-closed containers. Ophthalmic solutions should be protected from light.

3.4.4 Bioavailability

No data available.

3.4.5 Specific properties and composition

No data available.

4. USES

4.1 Indications

Oral administration

Timolol has been used in the treatment of hypertension, angina pectoris, cardiac arrhythmias, migraine and for the reduction of mortality following myocardial infarction.

Ocular administration

Ophthalmic solutions of **timolol** are used in the treatment of glaucoma to reduce intraocular pressure.

4.2 Therapeutic dosage

4.2.1 Adults

Ophthalmic solutions: The dose for glaucoma is 1 drop of 0.25% solution in each eye twice daily. Dosage may be

increased to 1 drop of 0.5% solution twice daily.

Oral doses in hypertension are 15 to 60 mg daily.

No dose adjustment is required in renal failure or in patients undergoing dialysis.

4.2.2 Children

Timolol is not recommended in children. The paediatric dose is unknown.

4.3 Contraindications

Timolol is contraindicated in patients with asthma, 2nd and 3rd degree AV block, and cardiogenic shock.

Timolol should be used cautiously in patients with chronic obstructive pulmonary diseases, sinus bradycardia, cardiac failure, myasthenia gravis, Raynaud's syndrome.

Timolol should not be administered with other beta-blockers.

5. ROUTES OF ENTRY

5.1 Oral

Poisoning after ingestion of **timolol** tablets may occur but only one case has been actually reported.

5.2 Inhalation

No data available.

5.3 Dermal

No case reported.

5.4 Eye

Systemic toxic symptoms may occur after treatment with **timolol** eye drops.

5.5 Parenteral

No data available.

5.6 Other

No data available.

6. KINETICS

6.1 Absorption by route of exposure

Oral

Timolol is almost completely (90%) absorbed from the gastrointestinal tract. The **peak plasma concentration** occurs 0.5-3 hours after ingestion (Fourtillan et al, 1981). **Timolol** is subject to a moderate first pass effect (Tocco et al, 1975).

Ocular

The onset of the ocular hypotensive action occurs after 10-20 minutes and lasts for at least 24 hours. (Zimmerman & Kaufman,

1977b). **Timolol** is absorbed systemically; serum concentrations are 2-5 g/l (Affrime et al, 1980; Alvan et al, 1980).

6.2 Distribution by route of exposure

Oral

Bioavailability is about 60 % (Wilson et al, 1982).

Apparent volume of distribution is 1.3 - 1.7 L/kg (Vermeij et al, 1978; Wilson et al, 1982)

Plasma protein binding is approximately 10%.

Timolol crosses the placenta

Ocular

Timolol is distributed in conjunctiva, cornea, sclera, iris, aqueous humor, liver, kidney and lung.

Transdermal

After cutaneous application of **timolol** ointment, 50 to 60 % is abosrbed systemically (Vlasses et al, 1985)

6.3 Biological half-life by route of exposure

Oral

After oral administration, the half-life is 2.5 - 5 hours (Tocco et al, 1975; Vermeij et al, 1978; Else et al, 1978; Ishizaki and Tawara, 1978). The half-life varies according to genetic differences in hepatic metabolism: half-lives of 3.7 and 7.5 hours were reported in extensive and poor metabolisers, respectively (McGourty et al, 1985). The total body clearance is 463 ml/kg/hr (Wilson et al, 1982).

6.4 Metabolism

Oral

Timolol is extensively metabolized in the liver by hydrolytic cleavage of the morpholino ring with subsequent oxidation. Following an oral dose, 80 % is metabolized and 20% is eliminated unchanged in urine (Tocco et al, 1975). Metabolism is dependent on genetic polymorphism.

6.5 Elimination by route of exposure

Oral: Kidney

About 20% of the dose is eliminated unchanged in the urine and 40 to 60% as metabolites (Tocco et al, 1975).

Breast milk

Timolol is present in breast milk but the total amount of **timolol** ingested by an infant who is breast feeding is unlikely to cause any clinical effects. Following a maternal oral dose, the milk/**plasma** ratio is 0.80.

Ocular: Breast milk

Following ocular instilation, the **concentration** in breast milk was approximatively 6 times higher (5.6 ng/ml) than in serum (0.93 ng/ml) (Lustgarten and Podos, 1983). However, the total amount of **timolol** ingested by an infant who is breast feeding is unlikely to cause any clinical effects.

7. PHARMACOLOGY AND TOXICOLOGY

7.1 Mode of action

7.1.1 Toxicodynamics

At toxic doses, **timolol** may exert a pronounced negative chronotropic and negative inotropic cardiac effect.

7.1.2 Pharmacodynamics

The exact mechanism whereby **timolol** reduces ocular pressure is still not known. The most likely action is by decreasing the secretion of aqueous humor (Zimmerman et al, 1977)

At therapeutic doses, **timolol** slightly decreases heart rate, supraventricular conduction and cardiac output.

7.2 Toxicity

7.2.1 Human data

7.2.1.1 Adults

Only one case of acute poisoning with **timolol** (after ingestion of 300 mg) has been reported;

this patient showed moderately severe symptoms (Tisserand, 1982).

7.2.1.2 Children

An 18 month-old girl developed bradycardia, respiratory depression and cyanosis 30 minutes after the administration of **timolol** eye drops (Williams and Ginther, 1982).

7.2.2 Relevant animal data

The oral LD50 is 1190 mg/kg in mice and 900 mg/kg in rats (RTECS, 1980).

7.2.3 Relevant in vitro data

No data available.

7.3 Carcinogenicity

No data available.

7.4 Teratogenicity

No epidemiological studies of congenital abnormalities among infants born to women treated with **timolol** during pregnancy have been reported.

7.5 Mutagenicity

No data available.

7.6 Interactions

Sinus bradycardia has been reported after concomitant treatment with **timolol** eye drops and quinidine.

7.7 Main adverse effects

8. TOXICOLOGICAL ANALYSES AND BIOMEDICAL INVESTIGATIONS

8.1 Material sampling plan

8.1.1 Sampling and specimen collection

8.1.1.1 Toxicological analyses

8.1.1.2 Biomedical analyses

8.1.1.3 Arterial blood gas analysis

8.1.1.4 Haematological analyses

8.1.1.5 Other (unspecified) analyses

8.1.2 Storage of laboratory samples and specimens

8.1.2.1 Toxicological analyses

8.1.2.2 Biomedical analyses

8.1.2.3 Arterial blood gas analysis

8.1.2.4 Haematological analyses

8.1.2.5 Other (unspecified) analyses

8.1.3 Transport of laboratory samples and specimens

8.1.3.1 Toxicological analyses

8.1.3.2 Biomedical analyses

8.1.3.3 Arterial blood gas analysis

8.1.3.4 Haematological analyses

8.1.3.5 Other (unspecified) analyses

8.2 Toxicological Analyses and Their Interpretation

8.2.1 Tests on toxic ingredient(s) of material

8.2.1.1 Simple Qualitative Test(s)

8.2.1.2 Advanced Qualitative Confirmation Test(s)

8.2.1.3 Simple Quantitative Method(s)

8.2.1.4 Advanced Quantitative Method(s)

8.2.2 Tests for biological specimens

8.2.2.1 Simple Qualitative Test(s)

8.2.2.2 Advanced Qualitative Confirmation Test(s)

8.2.2.3 Simple Quantitative Method(s)

8.2.2.4 Advanced Quantitative Method(s)

8.2.2.5 Other Dedicated Method(s)

8.2.3 Interpretation of toxicological analyses

8.3 Biomedical investigations and their interpretation

8.3.1 Biochemical analysis

8.3.1.1 Blood, **plasma** or serum

Routine biochemical investigations (i.e. sodium, potassium, creatinine and/or urea, glucose).

8.3.1.2 Urine

8.3.1.3 Other fluids
8.3.2 Arterial blood gas analyses
Should be obtained on admission.
8.3.3 Haematological analyses
8.3.4 Interpretation of biomedical investigations
Following a single oral dose of 20 mg, the mean **peak plasma concentration** is 83 microgram/l (range: 50 - 103) (Fourtillan et al, 1981). The **plasma concentration** required for beta-blocking activity is estimated to be 5 - 10 microgram/l.
8.4 Other biomedical (diagnostic) investigations and their interpretation
8.5 Overall Interpretation of all toxicological analyses and toxicological investigations
8.6 References
9. CLINICAL EFFECTS
9.1 Acute poisoning
9.1.1 Ingestion
Only one case of acute poisoning of **timolol** following ingestion of 300 mg in a 24 year-old man has been reported. The patient showed moderately severe symptoms, including drowsiness, vertigo, headache, first-degree atrioventricular block (Tisserand, 1982).
9.1.2 Inhalation
No data available.
9.1.3 Skin exposure

No data available.
9.1.4 Eye contact
Adverse systemic effects have been reported after treatment with ophtalmic solutions of **timolol**. See section 7.7.
9.1.5 Parenteral exposure
No data available.
9.1.6 Other
No data available.
9.2 Chronic poisoning
9.2.1 Ingestion
No data available.
9.2.2 Inhalation
No data available.
9.2.3 Skin exposure
No data available.
9.2.4 Eye contact
Dryness of the eye has been reported in a man treated by **timolol** 75 mg daily (Frais and Batley, 1979)

Corneal anaesthesia was observed in a patient treated with **timolol** eye drops (Calissendorff, 1981).
9.2.5 Parenteral exposure
No data available.
9.2.6 Other
No data available.
9.3 Course, prognosis, cause of death
Only one case of acute poisoning following ingestion of 300 mg **timolol** in a 24 year-old man has been reported. The patient showed moderately severe symptoms: drowsiness, vertigo, headache, first degree atrioventricular block which was treated by atropine 1 mg and isoproterenol 5 mg. The patient recovered without sequelae (Tisserand, 1982). No deaths have been reported.
9.4 Systematic description of clinical effects
9.4.1 Cardiovascular
Acute

First-degree atrioventricular block has been reported after ingestion of 300 mg; blood pressure was 120/80 mmHg and the heart rate was 58/min (Tisserand, 1982).

Bradycardia, hypotension, atrioventricular block and congestive cardiac failure may occur after administration of **timolol**.

Chronic: No data available.

9.4.2 Respiratory

Acute

Reversible respiratory arrest was observed in a 62-year-old woman after instillation of **timolol** eye drops (Botet et al, 1986) and may occur after oral administration.

Bronchospasm may occur in susceptible patients after administration of **timolol**.

Chronic: No data available.

9.4.3 Neurological

9.4.3.1 CNS

Acute

Drowsiness, vertigo, headache have been reported in one case after ingestion of 300 mg (Tisserand, 1982).

Fatigue, confusion, depression, hallucinations have been reported after administration of **timolol**.

Chronic: No data available.

9.4.3.2 Peripheral nervous system

Acute

Worsening of myasthenia gravis may occur after administration of **timolol**.

Chronic: No data available.

9.4.3.3 Autonomic nervous system

Acute: Effects of beta-blockade.

Chronic: Effects of beta-blockade.

9.4.3.4 Skeletal and smooth muscle

No data available.

9.4.4 Gastrointestinal

Acute

Abdominal pain, nausea, vomiting and diarrhoea may occur after administration of **timolol** orally or as eye drops.

Chronic: No data available.

9.4.5 Hepatic

No data available.

9.4.6 Urinary

9.4.6.1 Renal

No data available.

9.4.6.2 Other

No data available.

9.4.7 Endocrine and reproductive systems
No data available.
9.4.8 Dermatological
Acute: Urticaria may be observed.

Chronic: No data available.
9.4.9 Eye, ear, nose, throat: local effects
Acute

Eyelid erythema and oedema has been reported following ocular administration.

Chronic: No data available.
9.4.10 Haematological
No data available.
9.4.11 Immunological
No data available.
9.4.12 Metabolic
9.4.12.1 Acid-base disturbances
No data available.
9.4.12.2 Fluid and electrolyte disturbances
Hyperkalaemia has been reported.
9.4.12.3 Others
No data available.
9.4.13 Allergic reactions
No data available.
9.4.14 Other clinical effects
Sexual dysfunction following usual doses of topical ocular **timolol** has been reported and may also occur after oral administration.
9.4.15 Special risks
Timolol is eliminated in breast milk but the total amount of **timolol** ingested by an infant who is breast feeding is unlikely to cause clinical effects.

No epidemiological studies of congenital anomalies among infants born to women treated with **timolol** during pregnancy have been reported.

9.5 Other
No data available.
9.6 Summary
10. MANAGEMENT
10.1 General principles
Patients with poisoning by ingestion of **timolol** should be monitored preferably in an intensive care unit.

Monitor vital signs: ECG, blood pressure, respiration.

Treatment may include:

emesis, gastric lavage, oral activated charcoal

atropine for symptomatic bradycardia, isoproterenol and/or glucagon for atrioventricular block or hypotension

10.2 Relevant laboratory analyses
10.2.1 Sample collection
10.2.2 Biomedical analysis
10.2.3 Toxicological analysis
Measurement of **plasma timolol** concentrations is not useful for the clinical management.
10.2.4 Other investigations
10.3 Life supportive procedures and symptomatic/specific treatment

See also monograph on PROPRANOLOL.

Cardiovascular disturbances:

Sinus bradycardia may be treated with intravenous atropine.

Isoproterenol is the drug of choice for the treatment of atrioventricular block. Hypotension may require administration of isoproterenol or glucagon.

Respiratory:

Bronchospasm may be treated with beta-2-agonists or aminophylline.

10.4 Decontamination

Although emesis, gastric lavage and oral activated charcoal have not been evaluated in **timolol** poisoning but they may be indicated in poisoning by ingestion.

10.5 Elimination

The efficacy of forced diuresis has not been evaluated.

The elimination of **timolol** is not significantly enhanced by haemodialysis or peritoneal dialysis and these procedures cannot be recommended.

10.6 Antidote treatment

10.6.1 Adults

10.6.2 Children

10.7 Management discussion

11. ILLUSTRATIVE CASES

11.1 Case reports from literature

Tisserand (1982) reported a case of acute poisoning after ingestion of 300 mg of **timolol** in a 24 year-old man. The patient developed moderately severe symptoms, including drowsiness, vertigo, headache, first degree atrioventricular block. Treatment included atropine 1 mg and isoproterenol 5 mg. The patient recovered without any complications.

11.2 Internally extracted data on cases

11.3 Internal cases

12. Additional information

12.1 Availability of antidotes

No data available.

12.2 Specific preventive measures

No data available.

12.3 Other

No data available.

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See Also:
Toxicological Abbreviations

PDR Drug information for

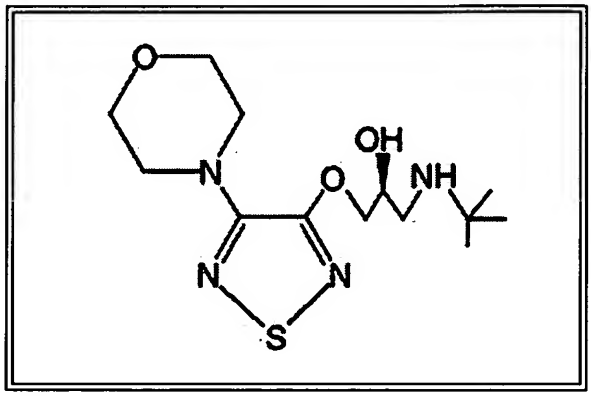
TIMOLOL HEMIHYDRATE

Manufacturer: Vistakon

DESCRIPTION

Betimol® (**timolol** ophthalmic solution), 0.25% and 0.5%, is a non-selective beta-adrenergic antagonist for ophthalmic use. The chemical name of the active ingredient is (S)-1-[(1,1-dimethylethyl) amino]-3-[[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl]oxy]-2-propanol. **Timolol** hemihydrate is the levo isomer. Specific rotation is $[(alpha)]^{25}_{405nm} = -16°$ (C=10% as the hemihydrate form in 1N HCl).

The molecular formula of **timolol** is Formula $C_{13}H_{24}N_4O_3S$ and its structural formula is:



Timolol (as the hemihydrate) is a white, odorless, crystalline powder which is slightly soluble in water and freely soluble in ethanol. **Timolol** hemihydrate is stable at room temperature.

Betimol® is a clear, colorless, isotonic, sterile, microbiologically preserved phosphate buffered aqueous solution.

It is supplied in two dosage strengths, 0.25% and 0.5%.

Each mL of Betimol® 0.25% contains 2.56 mg of **timolol** hemihydrate equivalent to 2.5 mg **timolol**.

Each mL of Betimol® 05% contains 5.12 mg of **timolol** hemihydrate equivalent to 5.0 mg **timolol**.

Inactive ingredients: monosodium and disodium phosphate dihydrate to adjust pH (6.5 - 7.5) and water for injection, benzalkonium chloride 0.01% added as preservative.

The osmolality of Betimol® is 260 to 320 mOsmol/kg.

CLINICAL PHARMACOLOGY

Timolol is a non-selective beta-adrenergic antagonist.

It blocks both beta $_1$ - and beta $_2$ -adrenergic receptors. **Timolol** does not have significant intrinsic sympathomimetic activity, local anesthetic (membrane-stabilizing) or direct myocardial depressant activity.

Timolol, when applied topically in the eye, reduces normal and elevated intraocular pressure (IOP) whether or not accompanied by glaucoma. Elevated intraocular pressure is a major risk factor in the pathogenesis of glaucomatous visual field loss. The higher the level of IOP, the greater the likelihood of glaucomatous visual field loss and optic nerve damage. The predominant mechanism of ocular hypotensive action of topical beta-adrenergic blocking agents is likely due to a reduction in aqueous humor production.

In general, beta-adrenergic blocking agents reduce cardiac output both in healthy subjects and patients with heart diseases. In patients with severe impairment of myocardial function, beta-adrenergic receptor blocking agents may inhibit sympathetic stimulatory effect necessary to maintain adequate cardiac function. In the bronchi and bronchioles, beta-adrenergic receptor blockade may also increase airway resistance because of unopposed parasympathetic activity.

Pharmacokinetics

When given orally, **timolol** is well absorbed and undergoes considerable first pass metabolism. **Timolol** and its metabolites are primarily excreted in the urine. The **half-life** of **timolol** in plasma is approximately 4 hours.

Clinical Studies

In two controlled multicenter studies in the U.S., Betimol® 0.25% and 0.5% were compared with respective **timolol** maleate eyedrops. In these studies, the efficacy and safety profile of Betimol® was similar to that of **timolol** maleate.

INDICATIONS AND USAGE

Betimol® is indicated in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

CONTRAINDICATIONS

Betimol® is contraindicated in patients with overt heart failure, cardiogenic shock, sinus bradycardia, second- or third-degree atrioventricular block, bronchial asthma or history of bronchial asthma, or severe chronic obstructive pulmonary disease, or hypersensitivity to any component of this product.

WARNINGS

As with other topically applied ophthalmic drugs, Betimol® is absorbed systemically. The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory and cardiac reactions, including death due to bronchospasm in patients with asthma, and rarely, death in association with cardiac failure have been reported following systemic or topical administration of beta-adrenergic blocking agents.

Cardiac Failure: Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe cardiac failure.

In patients without a history of cardiac failure, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. Betimol® should be discontinued at the first sign or symptom of cardiac failure.

Obstructive Pulmonary Disease: Patients with chronic obstructive pulmonary disease (e.g. chronic bronchitis, emphysema) of mild or moderate severity, bronchospastic disease, or a history of bronchospastic disease (other than bronchial asthma or a history of bronchial asthma which are contraindications) should in general not receive beta-blocking agents.

Major Surgery: The necessity or desirability of withdrawal of beta-adrenergic

blocking agents prior to a major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have been subject to protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, gradual withdrawal of beta-adrenergic receptor blocking agents is recommended. If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of beta-adrenergic agonists.

Diabetes Mellitus: Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

Thyrotoxicosis: Beta-adrenergic blocking agents may mask certain clinical signs (e.g. tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents which might precipitate a thyroid storm.

PRECAUTIONS

General

Because of the potential effects of beta-adrenergic blocking agents relative to blood pressure and pulse, these agents should be used with caution in patients with cerebrovascular insufficiency. If signs or symptoms suggesting reduced cerebral blood flow develop following initiation of therapy with Betimol®, alternative therapy should be considered.

There have been reports of bacterial keratitis associated with the use of multiple dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial suface. (See PRECAUTIONS , Information for Patients .)

Muscle Weakness: Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g. diplopia, ptosis, and generalized weakness). Beta-adrenergic blocking agents have been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

In angle-closure glaucoma, the goal of the treatment is to reopen the angle. This requires constricting the pupil. Betimol® has no effect on the pupil. Therefore, if **timolol** is used in angle-closure glaucoma, it should always be combined with a miotic and not used alone.

Anaphylaxis: While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated accidental, diagnostic, or therapeutic challenge with such allergens. Such patients may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions.

The preservative benzalkonium chloride may be absorbed by soft contact lenses. Patients who wear soft contact lenses should wait 5 minutes after instilling Betimol® before they insert their lenses.

Information for Patients

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures.

Patients should also be instructed that ocular solutions can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and

subsequent loss of vision may result from using contaminated solutions. (See PRECAUTIONS , General .)

Patients requiring concomitant topical ophthalmic medications should be instructed to administer these at least 5 minutes apart.

Patients with bronchial asthma, a history of bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, second- or third-degree atrioventricular block, or cardiac failure should be advised not to take this product (See CONTRAINDICATIONS .)

Drug Interactions

Beta-adrenergic blocking agents: Patients who are receiving a beta-adrenergic blocking agent orally and Betimol® should be observed for a potential additive effect either on the intraocular pressure or on the known systemic effects of beta-blockade.

Patients should not usually receive two topical ophthalmic beta-adrenergic blocking agents concurrently.

Catecholamine-depleting drugs: Close observation of the patient is recommended when a beta-blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

Calcium antagonists: Caution should be used in the co-administration of beta-adrenergic blocking agents and oral or intravenous calcium antagonists, because of possible atrioventricular conduction disturbances, left ventricular failure, and hypotension. In patients with impaired cardiac function, co-administration should be avoided.

Digitalis and calcium antagonists The concomitant use of beta-adrenergic blocking agents with digitalis and calcium antagonists may have additive effects in prolonging atrioventricular conduction time.

Injectable Epinephrine: (See PRECAUTIONS , General , Anaphylaxis .)

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity of **timolol** (as the maleate) has been studied in mice and rats. In a two-year study orally administrated **timolol** maleate (300mg/kg/day) (approximately 42,000 times the systemic exposure following the maximum recommended human ophthalmic dose) in male rats caused a significant increase in the incidence of adrenal pheochromocytomas; the lower doses, 25 mg or 100 mg/kg daily did not cause any changes.

In a **life** span study in mice the overall incidence of neoplasms was significantly increased in female mice at 500 mg/kg/day (approximately 71,000 times the systemic exposure following the maximum recommended human ophthalmic dose). Furthermore, significant increases were observed in the incidences of benign and malignant pulmonary tumors, benign uterine polyps, as well as mammary adenocarcinomas. These changes were not seen at the daily dose level of 5 or 50 mg/kg (approximately 700 or 7,000, respectively, times the systemic exposure following the maximum recommended human ophthalmic dose). For comparison, the maximum recommended human oral dose of **timolol** maleate is 1 mg/kg/day.

Mutagenic potential of **timolol** was evaluated *in vivo* in the micronucleus test and cytogenetic assay and *in vitro* in the neoplastic cell transformation assay and Ames test, In the bacterial mutagenicity test (Ames test) high concentrations of **timolol** maleate (5000 and 10,000 g/plate) statistically significantly increased the number of revertants in *Salmonella typhimurium* TA100, but not in the other three strains tested. However, no consistent dose-response was observed nor did the number of revertants reach the double of the control value, which is regarded as one of the criteria for a positive result in the Ames test. *In vivo* genotoxicity tests (the mouse micronucleus test and cytogenetic assay) and *in vitro* the neoplastic cell

transformation assay were negative up to dose levels of 800 mg/kg and 100 g/mL, respectively.

No adverse effects on male and female fertility were reported in rats at **timolol** oral doses of up to 150 mg/kg/day (21,000 times the systemic exposure following the maximum recommended human ophthalmic dose).

Pregnancy Teratogenic effects:

Category C: Teratogenicity of **timolol** (as the maleate) after oral administration was studied in mice and rabbits. No fetal malformations were reported in mice or rabbits at a daily oral dose of 50 mg/kg (7,000 times the systemic exposure following the maximum recommended human ophthalmic dose). Although delayed fetal ossification was observed at this dose in rats, there were no adverse effects on postnatal development of offspring. Doses of 1000 mg/kg/day (142,000 times the systemic exposure following the maximum recommended human ophthalmic dose) were maternotoxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at doses of 14,000 times the systemic exposure following the maximum recommended human ophthalmic dose in this case without apparent maternotoxicity.

There are no adequate and well-controlled studies in pregnant women. Betimol® should be used during pregnancy only it the potential benefit justifies the potential risk to the fetus.

Nursing mothers:

Because of the potential for serious adverse reactions in nursing infants from **timolol**, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric use:

Safety and efficacy in pediatric patients have not been established.

ADVERSE REACTIONS

The most frequently reported ocular event in clinical trials was burning/stinging on instillation and was comparable between Betimol® and **timolol** maleate (approximately one in eight patients).

The following adverse events were associated with use of Betimol® in frequencies of more than 5% in two controlled, double-masked clinical studies in which 184 patients received 0.25% or 0.5% Betimol®:

OCULAR:

Dry eyes, itching, foreign body sensation, discomfort in the eye, eyelid erythema, conjunctival injection, and headache.

BODY AS A WHOLE:

Headache.

The following side effects were reported in frequencies of 1 to 5%:

OCULAR:

Eye pain, epiphora, photophobia, blurred or abnormal vision, corneal fluorescein staining, keratitis, blepharitis and cataract.

BODY AS A WHOLE:

Allergic reaction, asthenia, common cold and pain in extremities.

CARDIOVASCULAR:

Hypertension.

DIGESTIVE:

Nausea.

METABOLIC/NUTRITIONAL:

Peripheral edema.

NERVOUS SYSTEM/PSYCHIATRY:

Dizziness and dry mouth.

RESPIRATORY:

Respiratory infection and sinusitis.

In addition, the following adverse reactions have been reported with ophthalmic use of beta blockers:

OCULAR:

Conjunctivitis, blepharoptosis, decreased corneal sensitivity, visual disturbances including refractive changes, diplopia and retinal vascular disorder.

BODY AS A WHOLE:

Chest pain.

CARDIOVASCULAR:

Arrhythmia, palpitation, bradycardia, hypotension, syncope, heart block, cerebral vascular accident, cerebral ischemia, cardiac failure and cardiac arrest.

DIGESTIVE:

Diarrhea.

ENDOCRINE:

Masked symptoms of hypoglycemia in insulin dependent diabetics (See WARNINGS).

NERVOUS SYSTEM/PSYCHIATRY:

Depression, impotence, increase in signs and symptoms of myasthenia gravis and paresthesia.

RESPIRATORY:

Dyspnea, bronchospasm, respiratory failure and nasal congestion.

SKIN:

Alopecia, hypersensitivity including localized and generalized rash, urticaria.

OVERDOSAGE

No information is available on overdosage with Betimol®. Symptoms that might be expected with an overdose of a beta-adrenergic receptor blocking agent are bronchospasm, hypotension, bradycardia, and acute cardiac failure.

DOSAGE AND ADMINISTRATION

Betimol® Ophthalmic Solution is available in concentrations of 0.25 and 0.5 percent. The usual starting dose is one drop of 0.25 percent Betimol® in the affected eye(s) twice a day. If the clinical response is not adequate, the dosage may be changed to one drop of 0.5 percent solution in the affected eye(s) twice a day.

If the intraocular pressure is maintained at satisfactory levels, the dosage schedule may be changed to one drop once a day in the affected eye(s). Because of diurnal variations in intraocular pressure, satisfactory response to the once-a-day dose is best determined by measuring the intraocular pressure at different times during the day.

Since in some patients the pressure-lowering response to Betimol® may require a few weeks to stabilize, evaluation should include a determination of intraocular pressure after approximately 4 weeks of treatment with Betimol®.

Dosages above one drop of 0.5 percent Betimol® twice a day generally have not been shown to produce further reduction in intraocular pressure, If the patient's intraocular pressure is still not at a satisfactory level on this regimen, concomitant therapy with pilocarpine and other miotics, and/or epinephrine, and/or systemically administered carbonic anhydrase inhibitors, such as acetazolamide can be instituted.

HOW SUPPLIED

Betimol® (**timolol** ophthalmic solution) is a clear, colorless solution.

Betimol® 0.25% is supplied in a white, opaque, plastic, ophthalmic dispenser bottle with a controlled drop tip as follows:

NDC 68669-522-05 5.0mL fill in 5 cc container

NDC 68669-522-10 10mL fill in 11 cc container

NDC 68669-522-15 15mL fill in 15 cc container

Betimol® 0.5% is supplied in a white, opaque, plastic, ophthalmic dispenser bottle with a controlled drop tip as follows:

NDC 68669-525-05 5.0mL fill in 5 cc container

NDC 68669-525-10 10mL fill in 11 cc container

NDC 68669-525-15 15mL fill in 15 cc container

Rx Only

STORAGE

Store between 15-30°C (59-86°F). Do not freeze. Protect from light.

MARKETED BY:

VISTAKON® Pharmaceuticals, LLC

Jacksonville, FL 32256 USA

MANUFACTURED BY:

Santen Oy, P.O. Box 33

FIN-33721 Tampere, Finland

Santen®

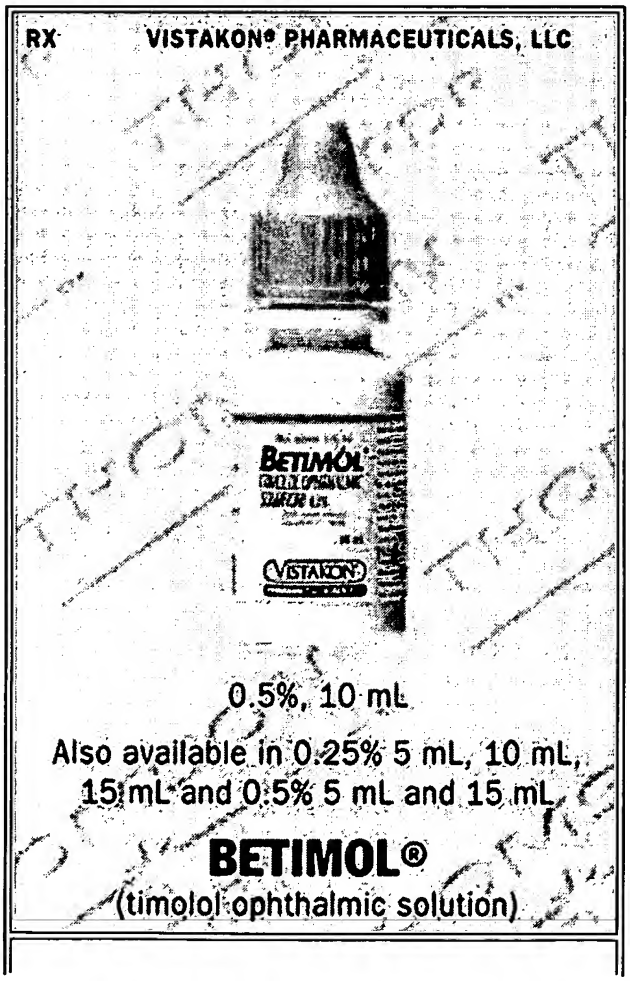
March 2004 Version

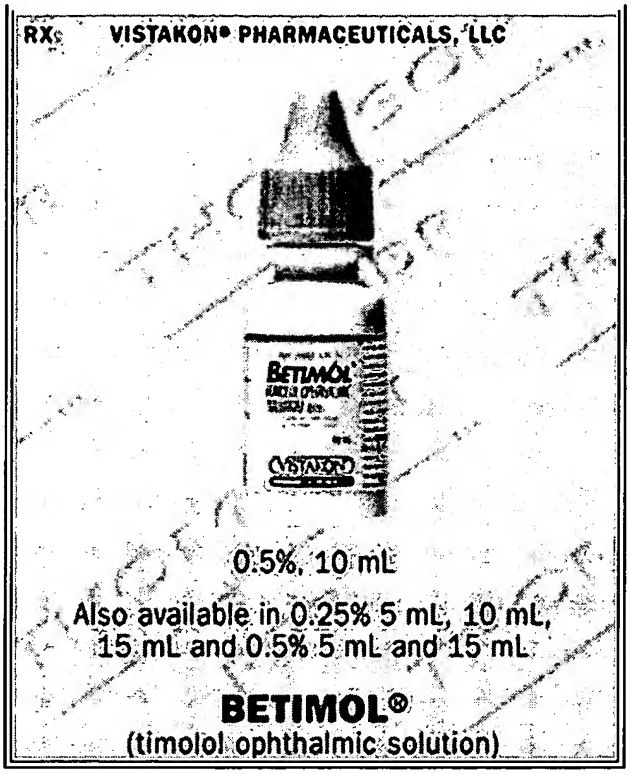
VISTAKON® Pharmaceuticals, LLC

PRODUCT PHOTO(S):

NOTE: These photos can be used only for identification by shape, color, and imprint. They do not depict actual *or relative* size.

The product samples shown here have been supplied by the manufacturer and reproduced in full color by **PDR** as a quick-reference identification aid. While every effort has been made to assure accurate reproduction, please remember that any visual identification should be considered preliminary. In cases of poisoning or suspected overdosage, the drug's identity should be verified by chemical analysis.





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